cobas® HPV Test

Microbiology Devices Panel

P100020/S008

March 12, 2014

Roche

cobas® HPV Test

Microbiology Devices Panel

P100020/S008

March 12, 2014

Roche

Introduction

Christoph Majewski, PhD

Lifecycle Leader, HPV and Microbiology
Roche Molecular Systems

Roche

Agenda

Introduction	**Christoph Majewski, PhD** Lifecycle Leader, HPV & Microbiology, RMS
Clinical Need for HPV as Primary Screening Test	**Thomas C. Wright, Jr., MD** Professor Emeritus, Columbia University
ATHENA Study Objectives and Statistics	**Abha Sharma**, **PhD** Director Biostatistics, RMS
Data from ATHENA Supporting cobas® HPV Test for Primary Screening	**Catherine Behrens, MD, PhD, FACOG** Director, Clinical Research, RMS
Clinical Implications and Benefit-Risk	**Thomas C. Wright, Jr., MD** Professor Emeritus, Columbia University
Summary	**Christoph Majewski, PhD** Lifecycle Leader, HPV & Microbiology, RMS

CI-3

Pap Test Revolutionized Cervical Cancer Screening, but Unmet Need Still Exists

- Screening significantly reduced cervical cancer incidence

- In 2014: ~12,360 cases and ~4020 deaths in the US

- Cytology and cotesting present standard of care

- Current solutions have limitations and are highly complex

- Primary HPV screening can address some limitations

CI-4

2

HPV Primary Screening
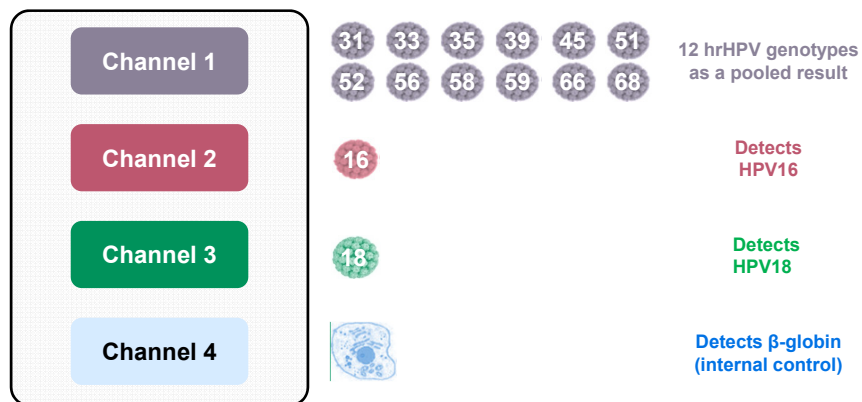### Proposed New Claim for cobas® HPV Test

- Use as first-line screening test in women 25 and older to detect high-risk HPV, including HPV genotypes 16 and 18

- **Candidate Algorithm: HPV Primary Screening with HPV 16/18 and Cytology Triage**

  - Negative for HPV: Follow-up by physician's judgment

  - Positive for HPV genotype 16/18: Colposcopy

  - Positive for any of 12 high-risk HPV types: Reflex to a cytology exam to determine need for colposcopy

CI-5

---

cobas® HPV Test Technology Overview
Approved in 2011 for ASC-US Triage and Cotesting

| Channel 1 | 31 33 35 39 45 51 52 56 58 59 66 68 | 12 hrHPV genotypes as a pooled result |
Channel 2	16	Detects HPV16
Channel 3	18	Detects HPV18
Channel 4		Detects β-globin (internal control)

4 channel design allows reporting of pooled hrHPV, as well as simultaneously providing HPV 16/18 specific identification from a single test tube

Wright TC Jr, et al. *Am J Obstet Gynecol* 2012; 206:46.e1-.e11

CI-6

Importance of Genotype
Prevalence of HPV16 and HPV18 in Cervical Cancer
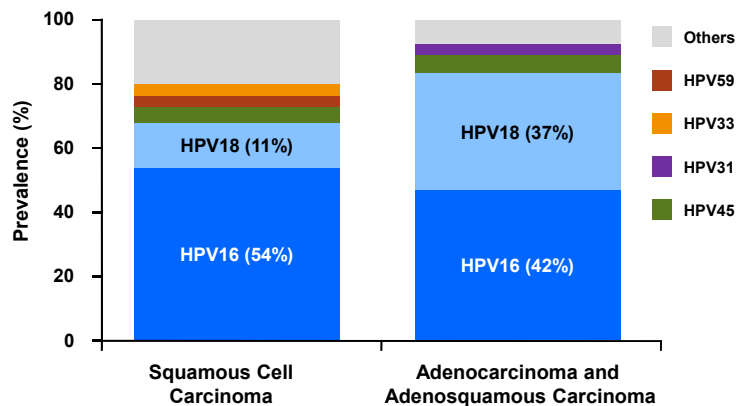
Approximately 70% of all cervical cancers are associated with HPV genotype 16 or 18

[1]Note distribution is for single infections only
Bosch FX, et al. *J Natl Cancer Inst Monogr* 2003; 31:3–13.

CI-7

cobas® HPV Test
Regulatory Background

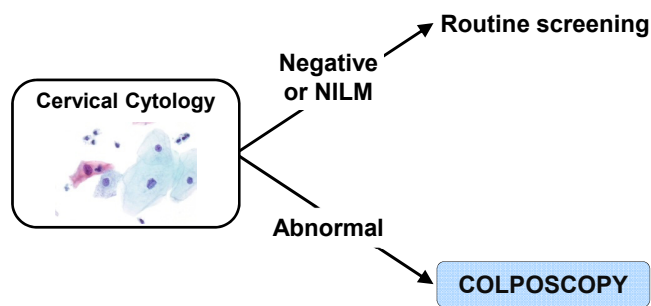CI-8

**Clinical Need for HPV
as Primary Screening Test**

Thomas C. Wright, Jr., MD

Professor Emeritus
Columbia University

Cytology-based Screening
Most Widely Utilized Globally and in the U.S.

Routine screening

Negative
or NILM

Cervical Cytology

Abnormal

COLPOSCOPY

This is our <u>Comparator Algorithm</u>

**Cervical cytology at 3 year intervals is considered an acceptable
approach by both the USPSTF and American Cancer Society**

Limitations of Cervical Cytology

- Interpretation is quite subjective which results in considerable intra- and inter-laboratory variation

- Relatively low sensitivity for the detection of high-grade cervical cancer precursors

- Identifies individuals with cancer precursors but not women at risk of developing cancer precursors

CC-11

Reproducibility of Cervical Cytology
Re-read of 4948 Liquid-based Cytology Slides

QC Reviewer's Diagnosis

Original Diagnosis	NILM	ASC-US	LSIL	≥HSIL
NILM	**78%**	19%	3%	<1%
ASC-US	39%	**43%**	17%	2%
LSIL	4%	22%	**68%**	6%
≥HSIL	3%	23%	27%	**47%**

Stoler and Schiffman *JAMA*, 2001.

CC-12

6

Variability of Cervical Cytology
ATHENA Results

	Lab A	Lab B	Lab C	Lab D
Number	12,294	4218	16,979	12,442
Median Age	40.9	37.9	39.3	40.1
≥ASC-US	3.8%	5.2%	8.1%	9.9%
Sensitivity of Cytology*	42.0	51.0	60.5	73.0
Sensitivity of cobas®*	90.1	88.2	88.4	88.9

*Note: for ≥CIN2
Wright et al. *Int. J. Cancer*, 2013. Oct 7 epub
Data not reviewed by the FDA

CC-13

Limitations of Cervical Cytology

- Interpretation is quite subjective which results in considerable intra- and inter-laboratory variation

- Relatively low sensitivity for the detection of high-grade cervical cancer precursors

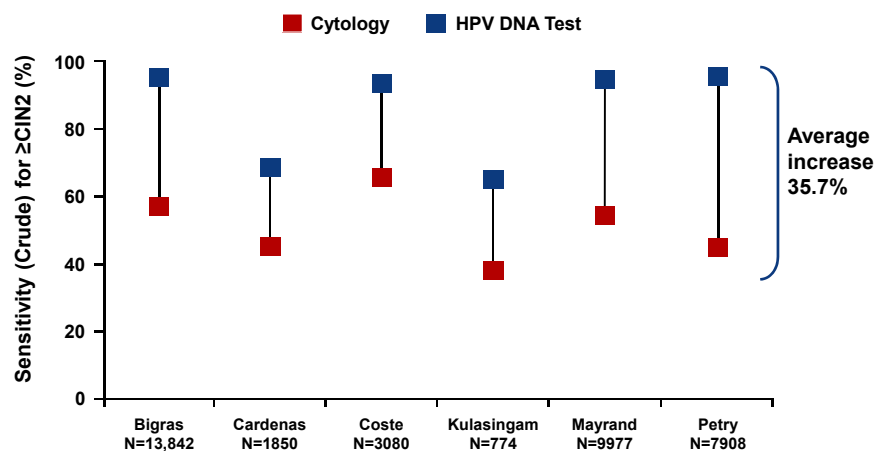- Identifies individuals with cancer precursors but not women at risk of developing cancer precursors

CC-14

Performance of Cervical Cytology
Sensitivity for ≥CIN2

Author	Year	Number	Method	Sensitivity	95% CI
Petry	2003	8466	Conv	44%	(30-58)
Coste	2003	3080	Conv	65%	(50-80)
Taylor	2005	3114	LBC	71%	(58-81)
Ronco	2006	22,760	LBC	74%	(62-84)
Mayrand	2007	10,153	Conv	57%	(34-78)

CC-15

Sensitivity of HPV to Detect ≥CIN2 is Higher than Cytology in USPSTF Review

HPV testing used an HPV assay other than cobas® HPV Test
Studies performed in developed countries in women 30 years and older
Whitlock EP, et al. *Ann Intern Med.*2011; 155:687–697, W214–5.

CC-16

Limitations of Cervical Cytology

- Interpretation is quite subjective which results in considerable intra- and inter-laboratory variation

- Relatively low sensitivity for the detection of high-grade cervical cancer precursors

- Identifies individuals with cancer precursors but not women at risk of developing cancer precursors

CC-17

10 Year Cumulative Risk of ≥CIN3 in Women ≥30 Years with NILM Cytology
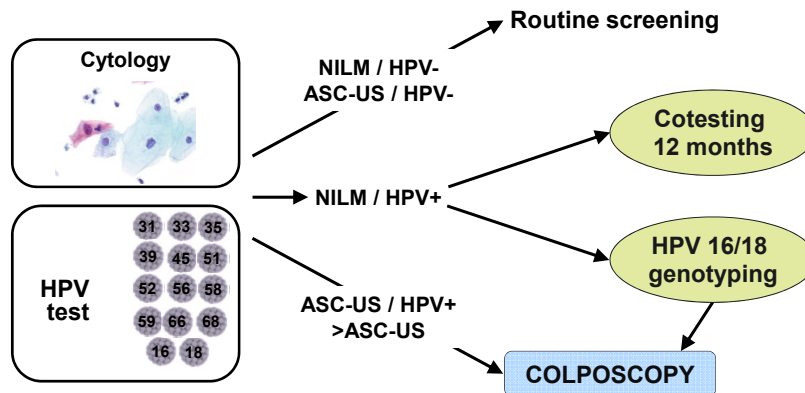## Kaiser Portland OR
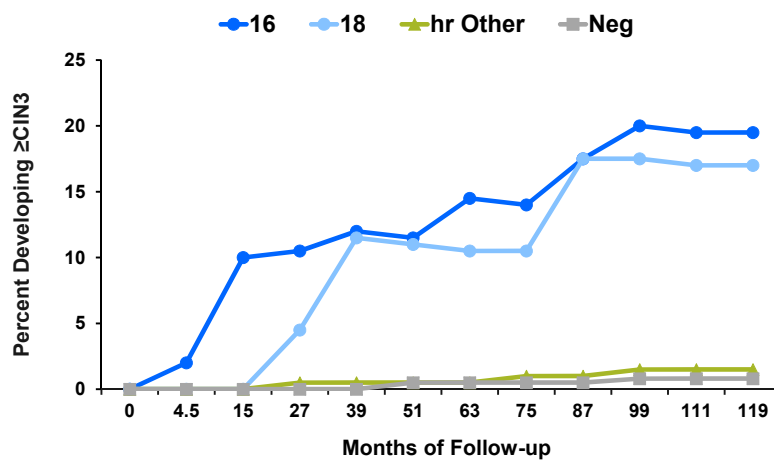
HPV testing used an HPV assay other than cobas® HPV Test
Kahn et al. *JNCI*, 2005: 97; 1072

CC-18

Cotesting with Cytology and HPV
**Used in the U.S. But Not the Predominant Method**

NILM / HPV-
ASC-US / HPV- → Routine screening

Cytology

HPV test
31 33 35
39 45 51
52 56 58
59 66 68
16 18

NILM / HPV+ → Cotesting 12 months

→ HPV 16/18 genotyping

ASC-US / HPV+
>ASC-US → COLPOSCOPY

CC-19

Large Number of Cytology Categories

NILM (negative)	**AGC-EC**
ASC-US	**AGC-EM**
ASC-H	**AIS**
LSIL	**Other**
HSIL	
Satisfactory	
Sat but limited by…	**Unsatisfactory**

2013 ASCCP Management Guidelines have 12 different algorithms just for cytology results
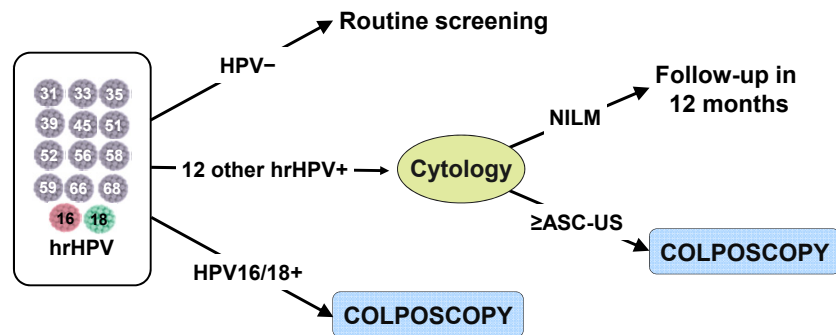
CC-20

Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*
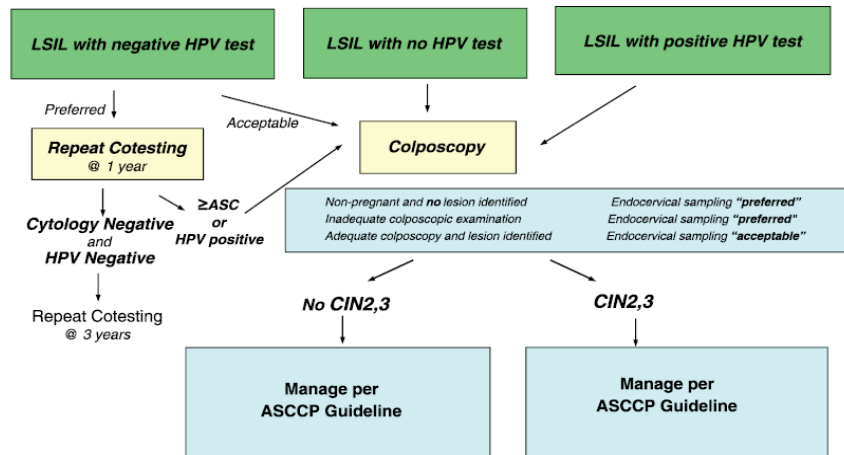
*Management options may vary if the women are pregnant or ages 21 to 24 years
Massad et al. *JLGTD*, 2013

CC-21

Primary HPV Screening – Candidate
### HPV with 16/18 Genotyping and Reflex Cytology

hrHPV=high risk HPV

CC-22

At What Age Should We Initiate Primary HPV Screening

- Current U.S. screening guidelines do not recommend cotesting for women 25-29 years of age

- Transient HPV infections are common in this age group and guideline makers did not want unnecessary follow-up examinations and colposcopy

- There is a high burden of CIN3 in women 25-29 years and cytology performs poorly in young as shown by UK screening audits

- In 2013 Kaiser Permanente, N. California reviewed their registry data and decided to begin cotesting at age 25 years
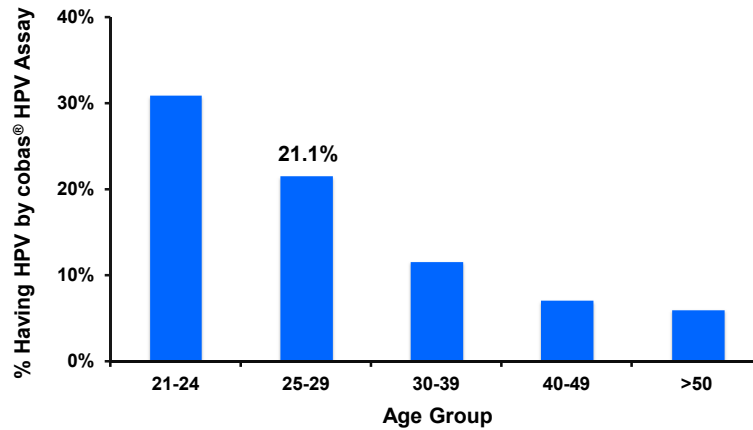
CC-23

Invasive Cervical Cancer in the U.S.
SEER Tumor Registry (1975-2010)
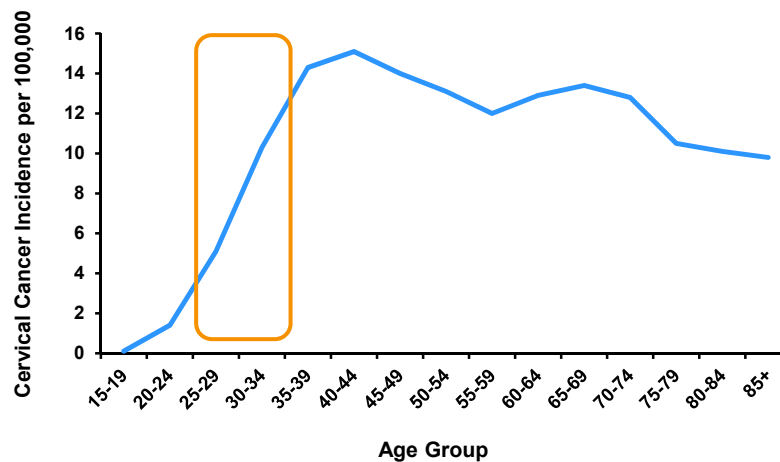
http://seer.cancer.gov/csr/1975_2010/

CC-24

HPV by Age Group
ATHENA

Data not reviewed by FDA
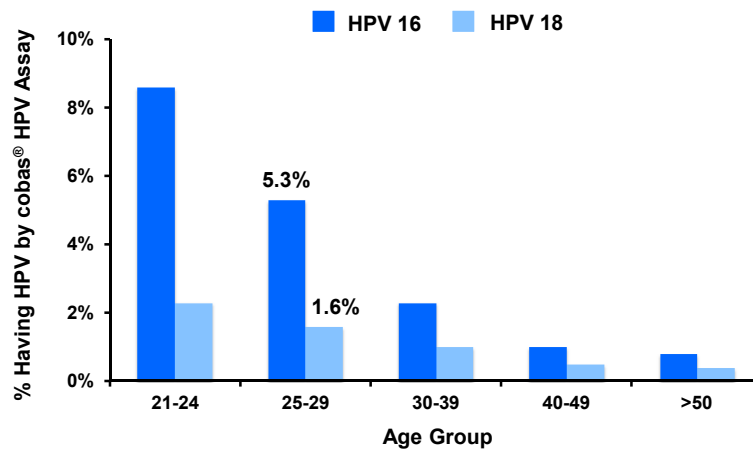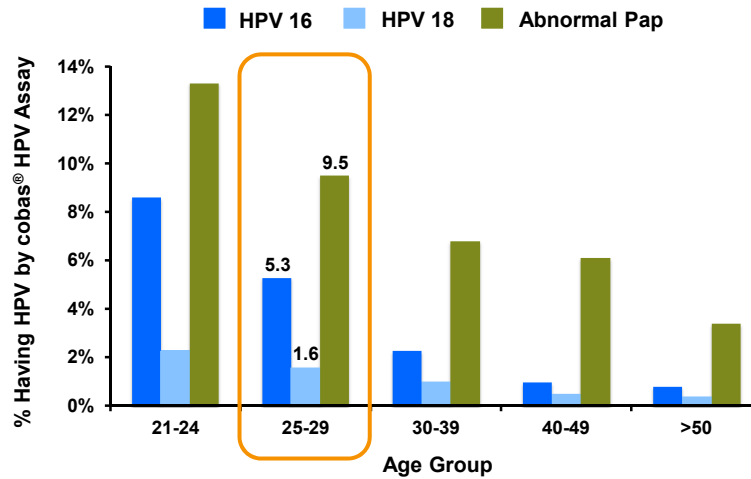Wright et al. *Am J Obst Gynecol*, 2011.

CC-25

HPV 16/18 by Age Group
ATHENA

Data not reviewed by FDA
Wright et al. *Am J Obst Gynecol*, 2011.

CC-26

HPV 16/18 vs ≥ASC-US
ATHENA

Data not reviewed by FDA
Wright et al. *Am J Obst Gynecol*, 2011.

CC-27

≥CIN3 by Age Group
ATHENA
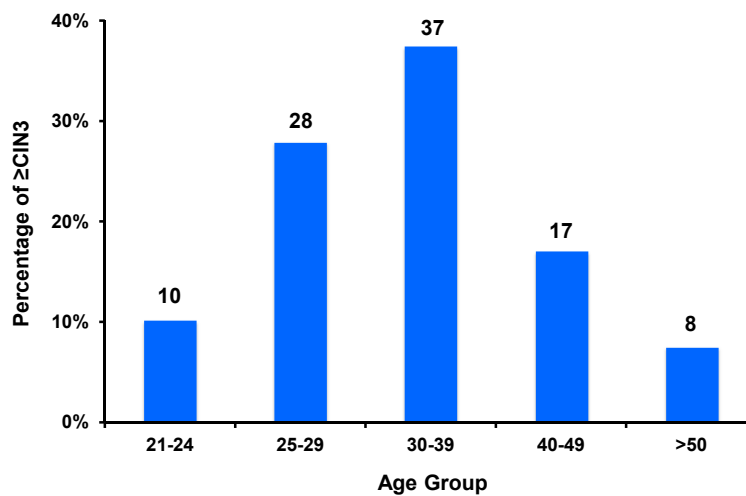
Data not reviewed by FDA
Wright et al. *Am J Obst Gynecol*, 2011.

CC-28

≥CIN3 by Age Group
ATHENA
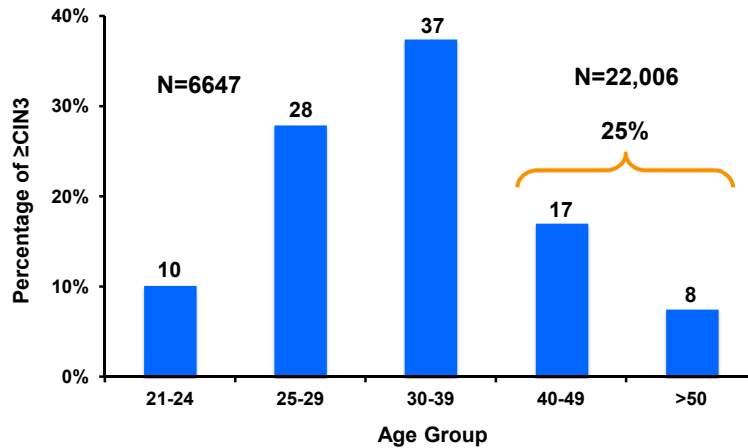
More ≥CIN3 disease in women 25-29 years than in women ≥40 years

Data not reviewed by FDA

CC-29

Proportion of Women with ≥CIN3 Who Have Negative Cytology (NILM)
ATHENA
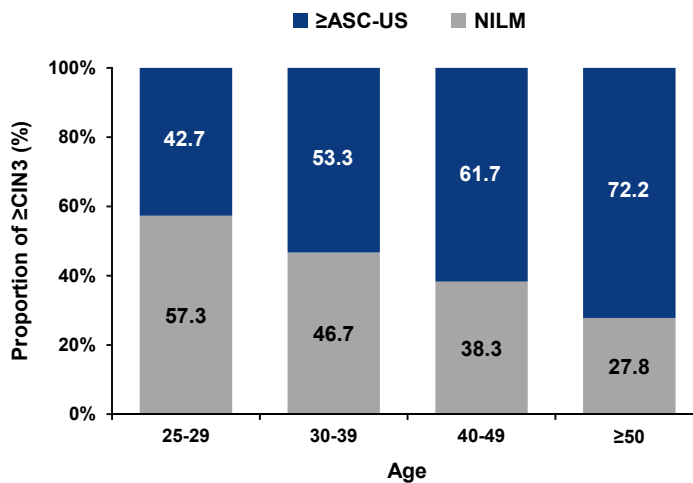
Data not reviewed by FDA
Percentages shown are for hrHPV+ women with ≥CIN3, N=252
Huh W, et al. 27th International Papillomavirus Conference, Berlin, Germany, September 17–22, 2011, OP-229.

CC-30

Need for Primary HPV Screening Starting at 25 Years of Age

- Cervical cytology appears to have reached the point where it alone is unable to reduce cervical cancer rates further

- Current management algorithms are extremely complicated and this confusion is potentially resulting in poor clinical care

- Cytology is not a good solution for identifying the majority of high-grade disease in women 25-29 years of age

CC-31

ATHENA Study Objectives and Statistics

Abha Sharma, PhD

Director, Biostatistics
Roche Molecular Systems

Roche

CT-32

Cervical Cancer Screening Evaluation
Study Design Requirements

- Cervical cancer screening study must:

    – Be a large cross-sectional cohort with sufficient follow-up for safety

    – Have sufficient cases of ≥CIN2

    – Be representative of target population

    – Adjust for verification bias

CT-33

Study Objectives and Screening Algorithms

- **Study Objective**: Compare the performance of primary HPV screening algorithm vs algorithm using cytology as first line of screening

- **Candidate Algorithm**: Primary HPV with 16/18 genotyping and reflex cytology

- **Comparator Algorithm**: Cytology alone (≥ASC-US to colposcopy)

- **Additional Comparator**: ATRI NM ≥30 GT

    – ASC-US Triage in women 25-29

    – Cotesting with genotyping in women ≥30

CT-34

17

Screening Algorithms
Performance Comparison

- **Endpoint**: ≥CIN2
- Secondary: ≥CIN3
  - Results presented for ≥CIN3 (better surrogate for cancer)
- **Performance Metrics**:
  - Sensitivity/specificity
  - PPV/NPV
  - Likelihood ratios PLR/NLR
- **Acceptance Criteria**: PLR/NLR
  - Higher PLR and Lower NLR indicate better performance
  - Confidence interval for the difference should exclude "0"

CT-35

Performance Estimates of Screening Algorithms
PLR, NLR

Parameter	Description	Interpretation
PLR >1	Se/(1-Sp)	1. How many times more likely women with ≥CIN3 are to have a positive result than women with <CIN3 2. Post-test odds = PLR × pre-test odds
NLR <1	(1-Se)/Sp	1. How many times less likely women with ≥CIN3 are to have a negative result than women with <CIN3 2. Post-test odds = NLR × pre-test odds

Note: PLR and NLR do not depend on the prevalence of disease

CT-36

Graphical Comparison of Algorithms

Superior

Better NPV

Sensitivity

Comparator Algorithm

Better PPV

Inferior

1-Specificity
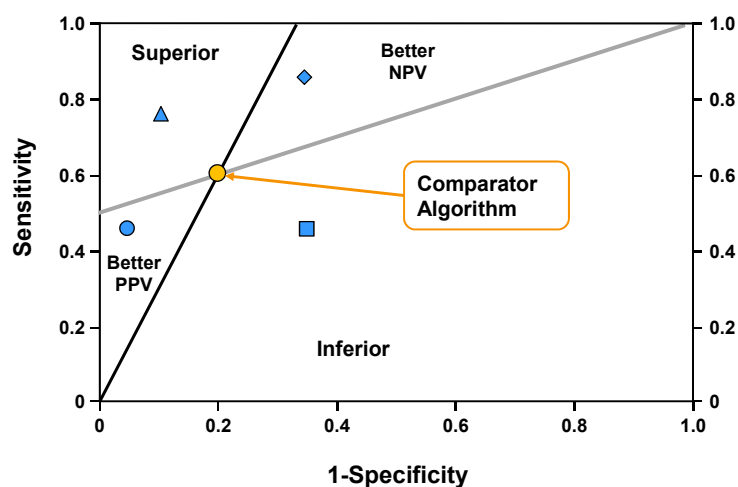
Kondratovich M. 2008; Biggerstaff BJ. 2000

CT-37

Statistical Methods for Baseline and Follow-up Verification Bias

- **Verification Bias:** Occurs when test results determine who is "verified" for disease status

    – Women with positive test results for HPV/cytology

    – A random subset of HPV/cytology negative patients randomized to colposcopy

- **Missing at Random** (MAR) assumption

- **VBA Calculations*:** Adjust performance statistics based on observed disease in verified group, using probability of being verified

*MS Pepe. 2002; XH Zhou et al. 2003; Begg and Greenes.1983

CT-38

19

ATHENA Study Objectives and Statistical Analysis
Conclusions

- Study Objective – Compare:
    - HPV as primary screening (Candidate)
    - Cytology as primary screening (Comparator)
- Verification Bias Adjusted (VBA) Statistics
- Acceptance Criteria
    - NLR for Candidate < NLR for Comparator
    - PLR for Candidate > PLR for Comparator
    - With additional information: Se/Sp and PPV/NPV
- Safety of negative HPV test result established by cumulative risk from 3 year follow-up

CT-39

Data from ATHENA Supporting cobas® HPV Test for Primary Screening

Catherine Behrens, MD, PhD, FACOG

Director, Clinical Research, RMS
Roche Molecular Systems

CA-40

The Challenge for ATHENA
Can We Improve Screening Methodology and Add Medical Value by Increasing Detection of Precancer?

- ATHENA is the largest prospective cervical cancer screening study in the U.S.

- Enrolled 47,208 women ≥21 years undergoing routine cervical cancer screening in the U.S.

  – 61 clinical sites in 23 states and 4 clinical laboratories

- Served as the registrational study for the cobas® HPV Test with 16/18 genotyping and FDA approval received in 2011 for:

  – ASC-US management

  – Cotesting with cytology for screening

CA-41

ATHENA Trial Design

- Specifically designed to demonstrate the performance of HPV testing in cervical screening in the U.S.

  – The ATHENA population was representative of a U.S. screening population in demographics, cytology distribution, and HPV prevalence

  – Both cytology and HPV testing (with genotyping) performed on all women

  – Rigorous disease ascertainment was achieved

    - All women who screened positive for either test (both Pap+ and HPV+) were taken to colposcopy

    - Histology determined by consensus of expert pathologists

CA-42

Demographics of ATHENA Trial Representative of the US Population (≥25)

Characteristics	Evaluable Subjects N=40,944 % (n)	U.S. Census Figures 2012[1] %
Age (years)	41	
Race		
White	83.4 (34,156)	79.8
American Indian or Alaskan Native	0.6 (226)	1.0
Black or African American	13.7 (5602)	12.4
Asian	1.6 (639)	5.2
Native Hawaiian/Other Pacific Islander	0.2 (98)	0.2
Any combination[1]	0.5 (220)	1.4
Missing	<0.1 (3)	
Ethnicity		
Hispanic or Latino	18.0 (7370)	12.9

Note: Any combination refers to subjects who selected more than one race
[1]Based on Annual Estimates of the Resident Population by Sex, Age, Race, and Hispanic Origin for the United States and States:
April 1, 2010 to July 1, 2012 (http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk)

CA-43

Cytology Results and Prevalence of hrHPV in ATHENA are Representative of a U.S. Screening Population

Pap Test Result	Eligible Subjects ≥25 Years N=40,944 % (n)	CAP 2010[1] %
NILM	93.5 (38,397)	91.5
ASC-US	4.0 (1632)	4.8
>ASC-US	2.4 (986)	3.6
LSIL	1.9	2.8
ASC-H	0.1	0.3
HSIL	0.3	0.4
Squamous Cell Carcinoma		
AGC[a, b]	<0.1	0.1

[1]CAP Cytopathology Checklist (all ages, not adjusted for ≥25 years)
[a]AGC (Atypical Glandular Cells) includes: AGC - Endocervical, AGC - Endometrial, and AGC - Not Otherwise Specified
[b]AGC, Favor Neoplastic includes: AGC - Endocervical - Favor Neoplastic
and AGC - Favor Neoplastic

CA-44

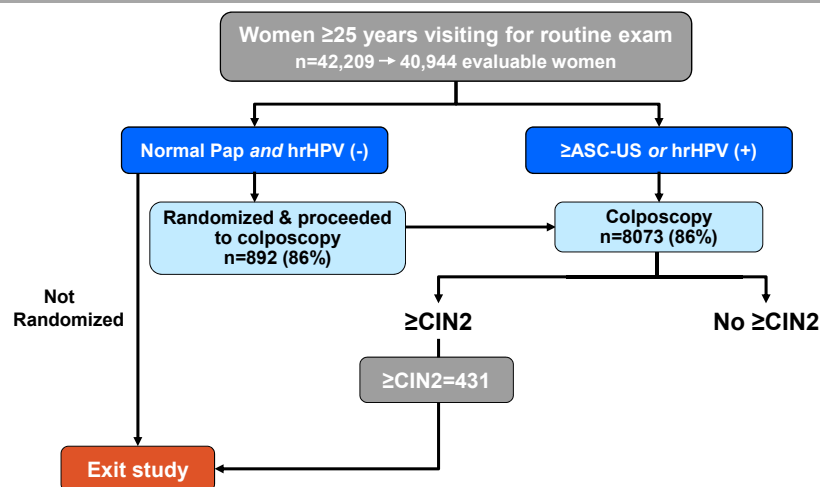## HPV Prevalence in ATHENA is Representative of a U.S. Population

Age Groups (Years)	HPV+ ATHENA %	HPV+ NMHPVPR* %	HPV16+ ATHENA %	HPV16+ NMHPVPR* %	HPV18+ ATHENA %	HPV18+ NMHPVPR* %
Overall Evaluable Primary Screening Subjects	10.5	14.2	2.1	3.1	0.8	0.9
25-29	21.1	21.8	5.3	5.2	1.6	1.4
30-49	9.4	11.5	1.7	2.2	0.7	0.7
≥50	6.0	6.9	0.8	1.3	0.4	0.5

*New Mexico HPV Pap Registry; assumed that carcinogenic HPV+ (HPV 16, 18, 31, 33, 39, 45, 52, 56, 58, 59, and 68) in NMHPVPR was equivalent to HPV+ (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66, and 68) in ATHENA
Wheeler et al. *International J Cancer*, 2013

CA-45

ATHENA Patient Flow
Cross-sectional Phase for Primary HPV Effectiveness

Women ≥25 years visiting for routine exam
n=42,209 → 40,944 evaluable women

Normal Pap *and* hrHPV (-)

≥ASC-US *or* hrHPV (+)

Randomized & proceeded to colposcopy
n=892 (86%)

Colposcopy
n=8073 (86%)

Not Randomized

≥CIN2

No ≥CIN2

≥CIN2=431

Exit study

CA-46

23

ATHENA Patient Flow
3 Year Follow-up Phase for Safety Evaluation

```
                    Exited after Baseline  ◄──  Colposcopy
                         n=1359                   n=8073

                                              N=6210

              ≥CIN2                                        No ≥CIN2

                       ≥CIN2=79   ◄------         Year 1 visit

                       ≥CIN2=35   ◄------         Year 2 visit

       Exit study  ◄──

                       ≥CIN2=42            Year 3
                                           exit colposcopy
                                           n=4063
```
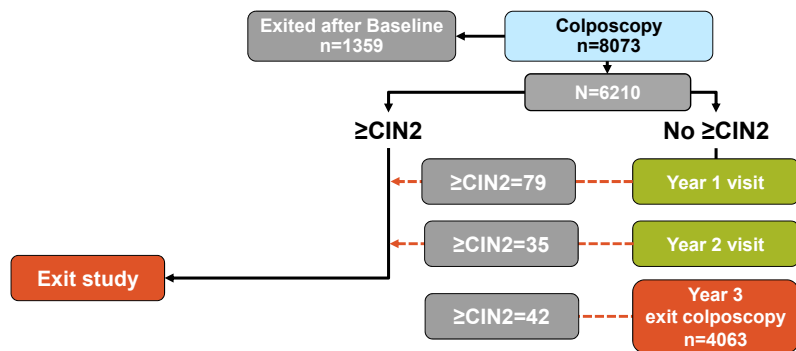
CA-47

Management of Cytology and Histology

Bethesda Classification	Management
Negative (NILM)	Routine follow-up 3 years
ASC-US	HPV testing
ASC-US/HPV−	Routine follow-up 3 years
ASC-US/HPV+	Colposcopy
LSIL	Colposcopy
HSIL	Colposcopy
ASC-H	Colposcopy
AGC	Colposcopy, endocervical curettage (ECC), endometrial biopsy
ACIS	Colposcopy, endocervical curettage (ECC), endometrial biopsy
Squamous/adenocarcinoma	Colposcopy

Histology

Negative

CIN1

CIN2 ┐
CIN3 │ "Precancer"
ACIS │
Invasive CA ┘
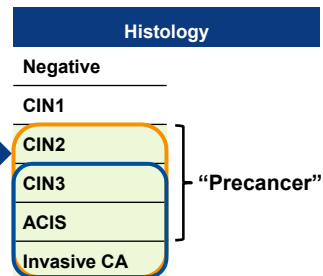
CA-48

3-Year Cumulative Risks for ≥CIN3
Primary Screening Population (≥25 Years)
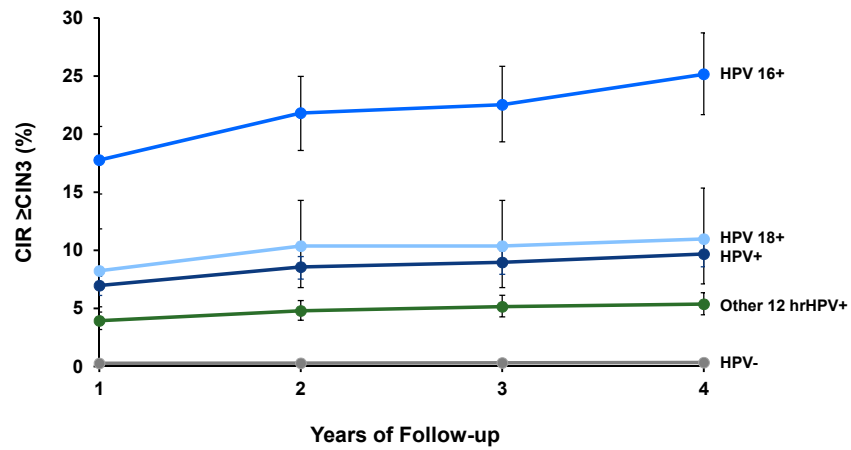
VBA estimates

CA-49

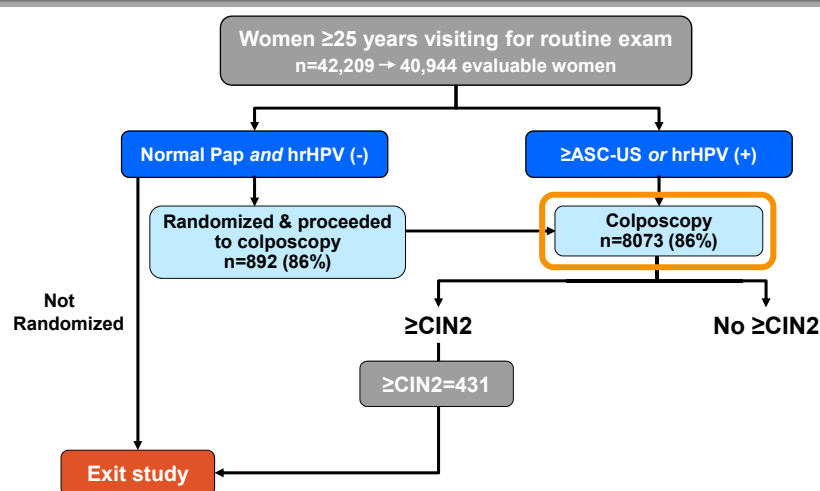# Primary Screening Algorithms

Effectiveness: Baseline Data

CA-50

25

Choosing the Optimal Screening Strategy

- Cervical cancer screening strategies should maximize disease detection (sensitivity), while minimizing the "harms"
- Colposcopy
  - Anxiety, discomfort
- Additional harms of screening
  - False negative results
    - Precancer missed by cytology
  - False positive results
    - Over-screening, over-management of lesions likely to regress
  - Treatment
    - Procedures (LEEP, conization) that may lead to longer-term complications related to pregnancy

CA-51

ATHENA Patient Flow
Cross-sectional Phase for Primary HPV Effectiveness

Women ≥25 years visiting for routine exam
n=42,209 → 40,944 evaluable women

Normal Pap *and* hrHPV (-) **≥ASC-US *or* hrHPV (+)**

Randomized & proceeded to colposcopy
n=892 (86%)

Colposcopy
n=8073 (86%)

Not Randomized

≥CIN2   No ≥CIN2

≥CIN2=431

Exit study

CA-52

ATHENA Data to be Presented

- Comparisons of the performance among 3 screening algorithms will be presented

  - Comparator (cytology alone) vs Candidate (HPV with 16/18 genotyping and reflex to cytology)

  - Additional Comparator: Cotesting

    - ATRI NM ≥30 GT (ASC-US Triage for women 25-29 years and cotesting for women ≥30 years): Current strategy supported by 2012 guidelines
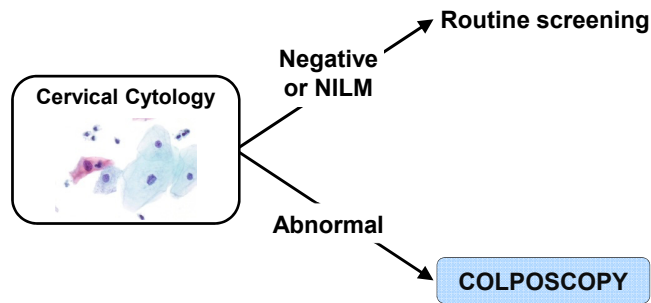
CA-53

ATHENA Data to be Presented

- To demonstrate effectiveness

  - Sensitivity, specificity, predictive values (PPV and NPV) and likelihood ratios (PLR and NLR)

- To demonstrate safety

  - Negative predictive value (NPV)

  - 3 Year cumulative risks (CIRs) for a negative HPV result vs negative cytology result at Baseline was calculated

- Only data using ≥CIN3 endpoint will be presented since ≥CIN3 is considered a better surrogate for cancer when assessing screening strategies
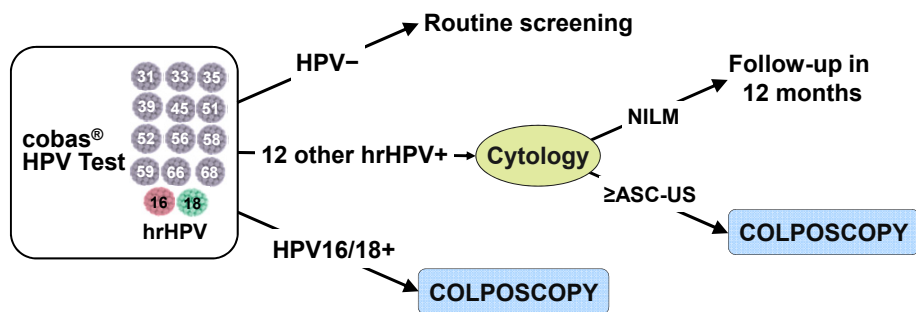
CA-54

Comparator Screening Algorithm
Cytology Alone

Cervical Cytology

Negative or NILM → Routine screening

Abnormal → COLPOSCOPY

CA-55

Candidate Screening Algorithm
HPV with 16/18 Genotyping and Reflex Cytology

cobas® HPV Test

31 33 35 39 45 51 52 56 58 59 66 68 16 18

hrHPV

HPV– → Routine screening

12 other hrHPV+ → Cytology
- NILM → Follow-up in 12 months
- ≥ASC-US → COLPOSCOPY

HPV16/18+ → COLPOSCOPY

hrHPV=high risk HPV

CA-56

Comparison of the Candidate vs Comparator (Cytology Alone) to Detect ≥CIN3

| | ≥CIN3 | |
Description	Relative Sensitivity[1] %	Relative Specificity[1] %
Comparator	1.00	1.00
Candidate	1.37*	1.02*

Using primary screening with the Candidate algorithm increases the sensitivity of HPV testing by 37% over cytology and raises the specificity to be at least equal to cytology

[1]Calculated as VBA sensitivity or specificity of Candidate/VBA sensitivity or specificity of Comparator
*Difference of VBA parameters statistically significant

CA-57

Comparison of Predictive Values and Likelihood Ratios of the Candidate and the Comparator to Detect ≥CIN3

| | ≥CIN3 | | | |
Description	PPV[1] %	NPV[1] %	PLR[1]	NLR[1]
Comparator	6.47	99.41	7.06	0.61
Candidate	12.25	99.58	14.24	0.44
Difference	5.78* (4.72, 6.94)	0.17* (0.12, 0.23)	7.18* (5.34, 9.4)	-0.17* (-0.24, -0.2)

The Candidate nearly doubles the PPV and PLR for detection of disease when compared to Cytology

The Candidate NPV and NLR also improve, indicating a superior measure of safety over Cytology
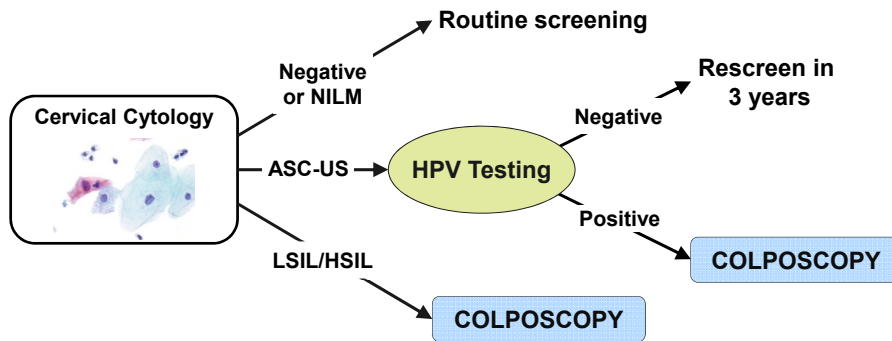
[1] Verification bias adjusted
*Difference of VBA parameters statistically significant

CA-58

29
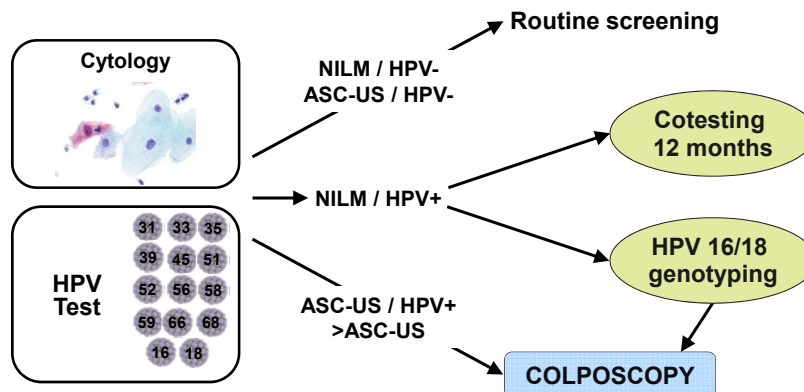
Comparison of the Performance of the Candidate vs Cotesting Hybrid to Detect ≥CIN3

Description	≥CIN3	
	Relative Sensitivity[1] %	Relative Specificity[1] %
Comparator	1.00	1.00
Candidate	1.37	1.02
ATRI NM ≥30 GT	1.25*	1.02

The sensitivity of Cotesting Hybrid ≥30 years decreases due to women 25-29 years having cytology screening only

[1]Calculated as VBA sensitivity or specificity of ATRI NM ≥30 GT/VBA sensitivity or specificity of Comparator
*Difference of VBA sensitivity statistically significant

CA-61

Comparison of Predictive Values and Likelihood Ratios of the Candidate and the Cotesting Hybrid

| Description	≥CIN3			
	PPV[1] %	NPV[1] %	PLR[1]	NLR[1]
ATRI NM ≥30 GT	11.04	99.52	12.66	0.49
Candidate	12.25	99.58	14.24	0.44
Difference	1.21* (0.46, 1.96)	0.06* (0.01, 0.09)	1.58* (0.62, 2.71)	-0.05* (-0.10, -0.01)

The PPV and NPV of the Candidate are superior, indicating significantly improved effectiveness and safety over the additional Comparator

[1] Verification bias adjusted
*Difference of VBA parameters statistically significant

CA-62

Comparison of Candidate and Additional Comparator with Comparator for ≥CIN3 Endpoint
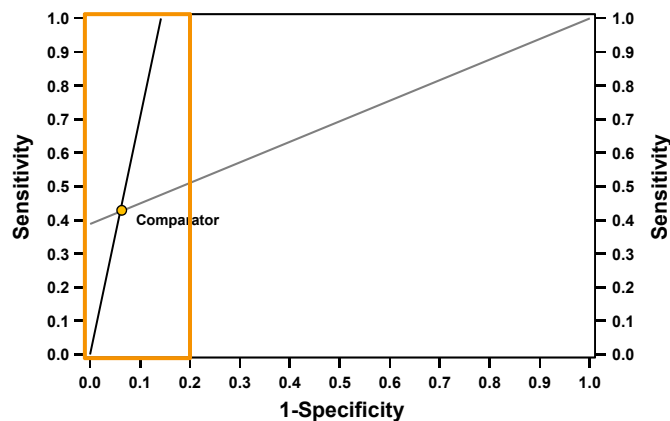
CA-63

Comparison of Candidate and Additional Comparators with Comparator for ≥CIN3 Endpoint

Superior Test

Better NPV

Candidate △
ATRI NM ≥30 ⬠

Comparator

Better PPV

Inferior Test
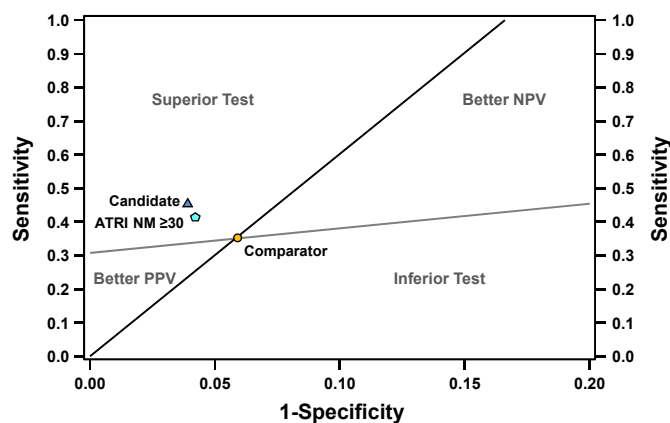
○ Comparator – Cytology Alone
△ Candidate – HPV 16/18 Genotyping Test with Reflex to Pap Test
⬠ ATRI NM ≥30 – ASC-US Triage 25-29 and ASC-US Triage NILM 16+/18+ 30+

CA-64

Clinical Implications for Various Algorithms

CA-65

Projected Measures of Clinical Management for Disease (≥CIN3)

Algorithm	Description	No. of Screening Tests	No. of Screening Tests Per ≥CIN3	No. of Colposcopies	No. of Colposcopies Per ≥CIN3	No. of ≥CIN3 Cases Detected[1]
Comparator	Cytology alone	40,944	239.4	2618	15.3	171
Candidate	HPV with 16/18 and reflex to cytology	44,057	189.9	1890	8.1	232
ATRI NM ≥30 GT	ASC-US Triage 25-29 and ASC-US Triage NILM 16+/18+ 30+yr	75,574	358.2	1916	9.1	211

CA-66

33

Summary of ATHENA Data in Support of Effectiveness of Screening

Roche

- When compared to cytology or cotesting:

  – Candidate demonstrates the best sensitivity for detection of ≥CIN3

  – The specificity of the Candidate is at least equal to cytology when 16/18 genotyping and reflex cytology is added to HPV as the primary screen

  – The Candidate PPV and PLR are 2x that of cytology and significantly greater than Cotesting Hybrid

  – The NPV and NLR of the Candidate are improved over both cytology and Cotesting Hybrid

  – The Candidate demonstrates a better balance of clinical resource management than either cytology or cotesting
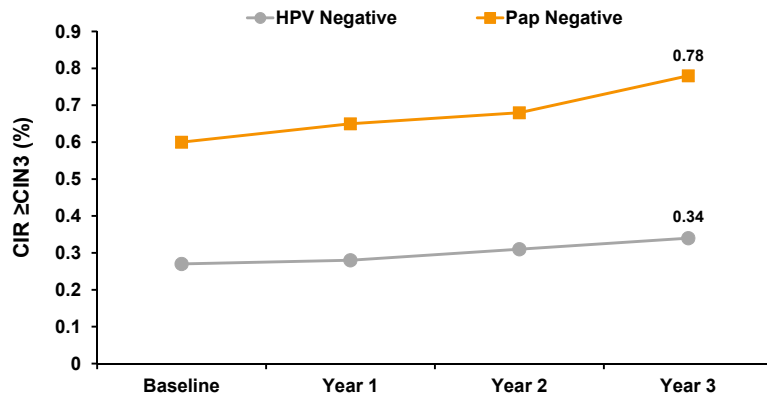
CA-67

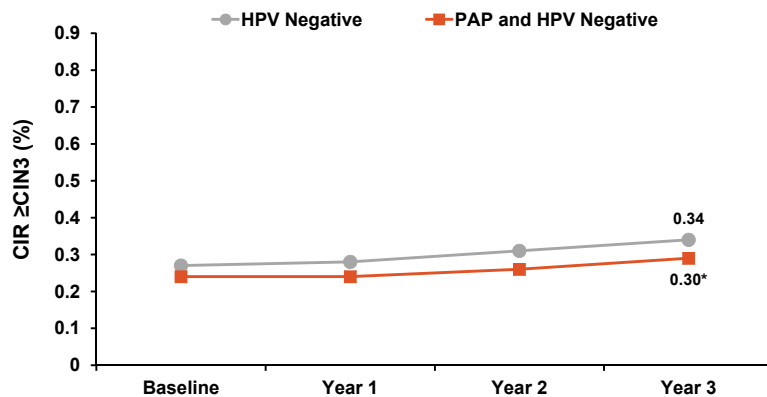# Primary Screening Algorithms

Safety: Longitudinal Data

Roche

CA-68

Evaluating the 90% of Women Who Screen HPV(-)

Legend: ● HPV Negative ■ Pap Negative

Y-axis: CIR ≥CIN3 (%), ranging 0 to 0.9

X-axis: Baseline, Year 1, Year 2, Year 3

Pap Negative line: Baseline 0.60, Year 3 0.78

HPV Negative line: Year 3 0.34

The lower risk of disease of a negative hrHPV at Baseline confirms the safety of a negative hrHPV result over 3 years

CA-69

The Benefit of Cotesting Over HPV in Reducing the 3 Year Risk of ≥CIN3 is Minimal

Legend: ● HPV Negative ■ PAP and HPV Negative

Y-axis: CIR ≥CIN3 (%), ranging 0 to 0.9

X-axis: Baseline, Year 1, Year 2, Year 3

HPV Negative line: Year 3 0.34

PAP and HPV Negative line: Year 3 0.30*

A negative Pap result added to a negative hrHPV result at Baseline adds little benefit and increases the colposcopy rate from 4.6% to 5.4%

* Statistically significant difference

CA-70

Sensitivity of cobas® HPV Test vs Cytology to Detect Invasive Cancer

	cobas® HPV Test+	Cytology+
ATHENA n=8	8	7
UNMHPVP Registry n=18[2]	17[1]	16
Total	25	23

- Sensitivity of cobas® HPV Test: 25/26 = 96.2%

- Sensitivity of cytology: 23/25 = 92%

[1] 1 case determined to be a poorly differentiated adenocarcinoma with origin uncertain, endocervical vs endometrial
[2] 1 case of endometrial cancer was found to have been sent in error after HPV testing was performed at RMS and 1 case was determined to be cobas® HPV "invalid" due to clotting of sample; these cases were excluded from the analysis

CA-71

Conclusions

- HPV-based strategies for primary screening are more sensitive for detection of high-grade disease than cytology-based strategies

  - The specificity of HPV-based strategies is increased by the addition of 16/18 genotyping and reflex testing to cytology

- Effectiveness of the Candidate algorithm is demonstrated by its superior performance compared to strategies supported by the current guidelines: Cytology alone and the Cotesting Hybrid

  - For the detection of precancer, the Candidate provides the optimal balance of benefits and harms

- Safety of the cobas® HPV Test as a primary screening test is confirmed by demonstrating that a negative HPV result at Baseline predicts a lower risk of ≥CIN3 at 3 years than a negative Pap result at Baseline

CA-72

Clinical Implications and Benefit-Risk

Thomas C. Wright, Jr., MD

Professor Emeritus
Columbia University

Candidate Algorithm
Discussion of Clinical Implications

- Screening for other cancers and STIs will **NOT** be adversely impacted if we use HPV alone for screening

- Shifting to primary HPV screening will **NOT** put women at increased risk for invasive cervical cancer or high-grade precursor lesions

Cervical Cytology to Screen for Other Gynecological Cancers

- The sensitivity of cervical cytology for endometrial and ovarian cancer is low (10-30% depending on study)[1,2]

- Positive cervical cytology is associated with high-stage disease or cervical involvement[2,3]

- Therefore, detecting endometrial or ovarian cancer by cervical cytology does not improve survival rates[2,3]

- Cervical cytology is not considered appropriate for screening for other cancers by **USPSTF, ACS, ACOG**

[1]Mitchell H. et al. *Int. J. Gyn.* Pathol. 1993; 12:34
[2]Nawanodi O. et al. *Arch. Gynecol. Obstet*. 2008; 277:171
[3]Roelofsoen T. et al. *Int. J. Gyn. Pathol.* 2013; 32:390

CR-75

Detection of Sexually Transmitted Infections with Cervical Cytology

- A number of organisms such as *T vaginalis, candida*, shift in flora suggestive of bacterial vaginosis, *actinomyces*, and Herpes Simplex can be identified on cervical cytology

- Sensitivity of cervical cytology is considered to be too low to be a useful screening test for infectious organisms – **CDC, ACOG, and other ID societies**

- There are other tests widely available to clinicians that are **BOTH** more sensitive and more specific for infectious organisms

CR-76

Candidate Algorithm
Discussion of Clinical Implications

- Screening for other cancers and STIs will **NOT** be adversely impacted if we use HPV alone for screening

- Shifting to primary HPV screening will **NOT** put women at increased risk for invasive cervical cancer or high-grade precursor lesions

CR-77

Sensitivity of Cytology and HPV for CIN3 and Cervical Cancer

- **NO screening test will detect ALL CIN3 or cancers**

    – Occasional sampling issues

    – Rare types of cervical cancer (mesonephric carcinoma, clear cell, etc) may not be caused by HPV

- Cervical cancer is uncommon which makes it hard to determine the sensitivity of any screening test

- The only accurate approach to evaluating the performance of screening tests for cancer is to use registry data and long-term follow-up studies

CR-78

Registry Data on Screening History of Women with Cervical Cancer

Description	No Recent Cytology* %	Cytology WNL (FN) %	Failure to Follow-up %
Kaiser[1]	56	32	13
Sweden[2]	64	24	11
Netherlands[3]	63	23	13
New Zealand[4]	51	37	12

* Different definitions in the different studies

[1]Leyden et al. *JNCI* 2005; 97:675
[2]Andrae et al. *JNCI* 2008; 100:622
[3]Gok et al. *BJC* 2011; 104:685
[4]Priest et al. *BJOG* 2007; 114:398

CR-79

Cytology in Cervical Cancer
Kaiser N. California Experience

- Reviewed screening histories of 965,360 women ≥30 years between 2003 and 2010

	SCC	AdenoCA
Total	198	114
NILM result	41 (20.7%)	52 (45.6%)
ASC-US / ASC-H	27 (13.6%)	14 (12.3%)
Other abnormal	130 (65.7%)	50 (43.9%)

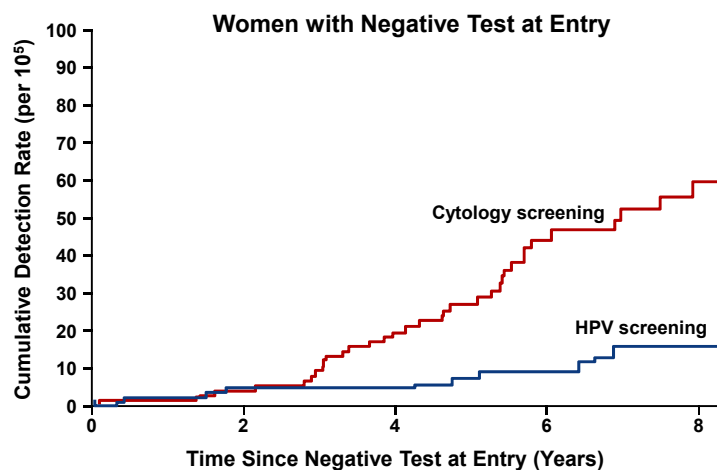Katki et al. *JLGTD* 2013; 17: S28

CR-80

HPV Testing Prevents Cervical Cancer

- We now have evidence that using HPV testing for screening reduces the incidence of invasive cervical cancer compared to cytology

- 4 European randomized trials conducted in Sweden, Netherlands, UK, and Italy

- Included 176,464 women 20-64 years of age

- Follow-up for a median of 6.5 years (1,214,415 person-years)

HPV testing used an HPV assay other than the cobas® HPV Test
Ronco et al. *Lancet* pub online, 2013

CR-81

HPV Testing vs Cytology for the Prevention of Cervical Cancer

Women with Negative Test at Entry

Cytology screening

HPV screening

Y-axis: Cumulative Detection Rate (per 10^5) — 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100

X-axis: Time Since Negative Test at Entry (Years) — 0, 2, 4, 6, 8

HPV testing used an HPV assay other than the cobas® HPV Test
Ronco et al. *Lancet* pub online, 2013

CC-82

Risk of ≥CIN3 After a Negative Screening Test
3 Years of Follow-up

	Pap	HPV	Cotest
Dillner et al.	0.50%	0.11%	0.06%
Katki et al.	0.17%	0.06%	0.05%
Rijkaart et al.	0.26%	0.06%	0.05%
ATHENA	0.78%	0.34%	0.30%

HPV testing used an HPV assay other than the cobas® HPV test (except ATHENA data)
Dillner et al. *BMJ* 2009;377; **21,351 women ≥20 years;** Katki et al. *Lancet Oncol.* 2011;12:663; **>300,000 women ≥30 years;** Rijkaart et al. *Br. J. Cancer* 2012;106:975; **>25,658 women 29-61 years;** ATHENA; **41,955 women ≥25 years**
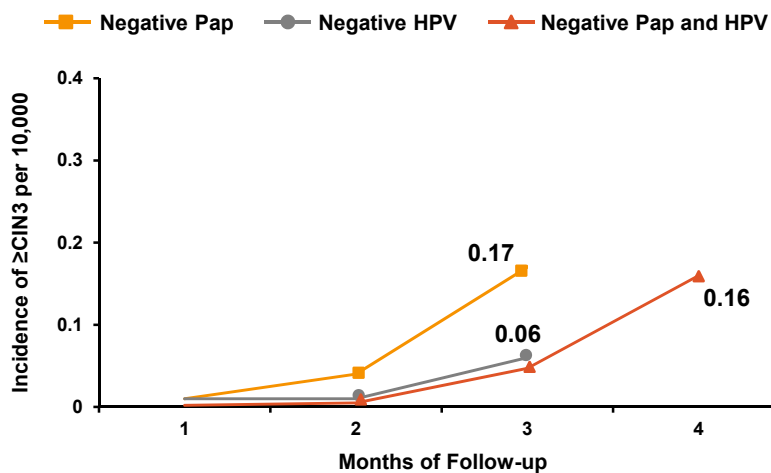
CR-83

Cumulative Incidence of ≥CIN3 in Kaiser
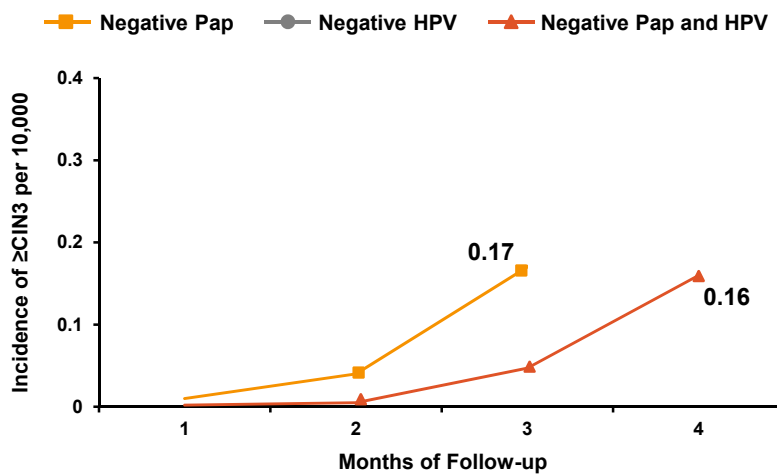
HPV testing used an HPV assay other than the cobas® HPV test
[1]Katki HA. et al. *Lancet Oncol.* 2011; 12:663

CR-84

Cumulative Incidence of ≥CIN3 in Kaiser

Negative Pap ■ **Negative HPV** ● **Negative Pap and HPV** ▲

Incidence of ≥CIN3 per 10,000

0.4

0.3

0.2 0.17

0.1 0.16

0.06

0

1 2 3 4

Months of Follow-up

HPV testing used an HPV assay other than the cobas® HPV test
[1]Katki HA. et al. *Lancet Oncol.* 2011; 12:663

CR-85

Summary
Discussion of Clinical Implications

- Using HPV alone will not adversely impact women with other gynecological cancers or STIs

- No screening test with acceptable specificity will detect all cervical cancers or precursors

- HPV alone offers greater protection against CIN3 and invasive cervical cancer than cytology alone – **widely used in the U.S.**

- Provides similar protection against CIN3 and invasive cervical cancer as cotesting

CR-86

Candidate Screening Algorithm
cobas® HPV with 16/18 Genotyping and Reflex Cytology
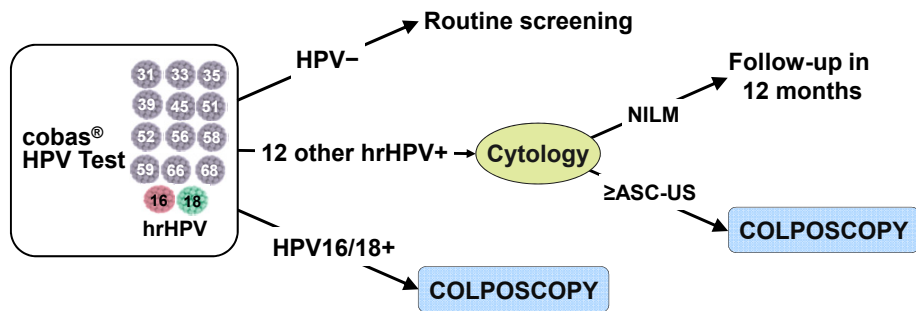
Detects significantly more disease than Comparator Algorithm (cytology alone) or Hybrid Cotesting

Greatly simplifies screening algorithms

CR-87

Summary

Christoph Majewski, PhD

Life Cycle Leader, HPV and Microbiology
Roche Molecular Systems

Roche

CS-88

Predictive Values and Likelihood Ratios of the Candidate, Comparator and ATRI NM ≥30 GT

	Detection of ≥CIN3				
	PPV %	NPV %	PLR	NLR	Colposcopy /≥CIN3
Candidate[1]	12.25	99.58	14.24	0.44	8.1
Comparator[1]	6.47*	99.41*	7.06*	0.61*	15.3*
ATRI NM ≥30 GT[1]	11.04*	99.52*	12.66*	0.49*	9.1*

3 year CIR of Candidate is 0.34 compared to 0.78 for cytology and 0.30 for cotesting (calculated for women ≥25 years)

[1]Verification bias adjusted
*Difference of VBA parameters statistically significant

CS-89